REMARKS

Unity of Invention

Applicant respectfully traverses the newly introduced lack of unity holding. The Examiner argues that claim 92 and claim 99 do not relate to a single general inventive concept under PCT Rule 31.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. The Examiner deems "methods for promoting angiogenesis comprising incubating a tissue with an HMGB1 protein" to be a potential common special technical feature which links the inventions. The Examiner takes the position that feature is shown in the prior art and thus cannot be a special technical feature under PCT Rule 13.2. Applicant respectfully submits that the Examiner's position is incorrect.

As discussed below Andersson alone or in combination with Okamoto and Kirkpatrick do not destroy unity of invention. Andersson et al. are totally silent about the use of HMGB1 as a drug and about the role of HMGB1 in promoting angiogenesis. Moreover, to the contrary there is a teaching away from combining Andersson et al. with the other cited documents of the prior art. Accordingly, the feature "methods for promoting angiogenesis comprising incubating a tissue with an HMGB1 protein" is not shown in the prior art and thus can be a special technical feature under PCT Rule 13.2.

In the light of the foregoing, the feature "methods for promoting angiogenesis comprising incubating a tissue with an HMGB1 protein" is a special technical feature which links the inventions of claim 92 and claim 99. Thus, claim 92 and claim 99 relate to a single general inventive concept under PCT Rule 13.1 and do not lack unity of invention

Rejected under 35 USC §103

Claims 92-94, 100 and 101 are Rejected under 35 USC §103 over Andersson *et al.* (J. Leukocyte Biol.) in view of Okamoto *et al.* (FASEB J.) and Kirkpatrick (Biomol. Eng.)

The Examiner argues that the subject matter of currently pending claims 92-94, 100 and 101 is obvious over Andersson et al. in view of Okamoto, and Kirkpatric. Applicant respectfully disagrees and submits that a *prima facie* of obviousness has been established.

In addressing the requirements for making, and sustaining an obviousness rejection, the Supreme Court de stated in *KSR v. Teleflex*:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn* stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.

The Office Action admits that "Andersson et al. do *not* explicitly teach (i) the effect of HMGB1 proteins in promotion of angiogenesis recited in claims 92 to 94...". Office Action at page 9. The patent office attempts to find that missing teachings in Okamoto; however, in doing so the patent office relies upon conclusory statements that lack a rational underpinning.

A skilled artisan would understand that Andersson teaches HMGB1is a potent pro-inflammatory cytokine that acts as a strong mediator of macrophage activation (Andersson et al., p.1085, right column, 2nd complete paragraph). Stimulated macrophages actively secrete HMGB1 to promote inflammation and in turn, stimulate production of multiple, proinflammatory cytokines (abstract). The Office Action points to nothing in Okamoto to indicate that the angiogenesis effects observed *in vitro* with glycer-AGE or glycol-AGE would occur *in vivo* where Andersson makes clear that a pro-inflammatory environment is promoted by HMGB1. In addition, the Office Action appears to presume only a single and common pathway for HMGB1 and glycer-AGE or glycol-AGE exists. Under the circumstances, the suggestion that the results observed by Okamoto *in vitro* would be observed *in vivo* is nothing more than a conclusory statement that lacks a rational underpinning. Moreover, it cannot even be concluded that by combining the references a predictable result would be obtained. For at least those reasons, a *prima facie* case capable of supporting a legal conclusion of obviousness has ***not*** been set forth.

Applicant further submits that Andersson teaches away from the use of HMGB1 in methods of promoting angiogenesis in a tissue, and from combining Andersson with a reference that might suggest such a use. HMGB1 is a potent pro-inflammatory cytokine that acts as a

strong mediator of macrophage activation (Andersson et al., p.1085, right column, 2nd complete paragraph). Stimulated macrophages actively secrete HMGB1 to promote inflammation, and in turn, stimulate production of multiple proinflammatory cytokines (abstract). Andersson et al. conclude that HMGB1 is a potent therapeutic **target** rather than considering HMGB1 as a drug which can be taken/administered (see page 1089, right column, which describes the "opportunity" to successfully treat experimental sepsis by late administration of neutralizing HMGB1 antibodies). That Andersson views HMGB1 as a therapeutic target is also emphasized by the teachings of the paragraph under the title "Lung inflammation" on page 1089, right column (Andersson et al.). From that discussion in Andersson, a skilled artisan would understand that a) administration of HMGB1 leads to cytokine production, b) HMGB1, subsequently, mediates acute inflammatory lung injury and c) HMGB1 is a target for anti-HMGB1 antibodies.

In light of the foregoing, Applicant further submits that a person skilled in the art would have seen no cause to use HMGB1 as a drug. This holds true although Okamoto et al. teach that AGE proteins elicit changes associated with angiogenesis and Andersson et al. teach that HMGB1 is a ligand for RAGE binding. Taking Andersson et al. as a starting point, a person skilled in the art aware of Okamoto et al. would not use HMGB1 as a drug, but would instead search for a drug targeting HMGB1. In deed, Andersson et al. even speculate about the latter as the last paragraph on page 1090 reads as follows:

> "Will HMGB1 be validated as a clinical target, like TNF or IL-1, to modulate acute or chronic inflammation, or will it be too dangerous to interfere with a molecule that is so central for the interplay between necrotic cell death with subsequent inflammation and repair responses?

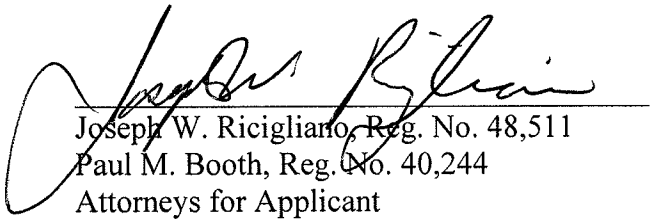
CONCLUSION

In view of the foregoing, applicant respectfully requests withdrawal of all rejections and objections of record and the issuance of a notice of allowance at the earliest possible time.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be

required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-2283.

Respectfully submitted,



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